Early Versus Late Recombinant Factor VIIa in Combat Trauma Patients Requiring Massive Transfusion

Jeremy G. Perkins, MD, Martin A. Schreiber, MD, Charles E. Wade, PhD, and John B. Holcomb, MD

Background: **Coagulopathy is a consequence of severe trauma, especially in massively transfused patients (≥10 units of red blood cells in 24 hours), and is associated with increased mortality. We hypothesized that recombinant factor VIIa (rFVIIa) administered to massive transfusion patients before transfusion of 8 units of blood (early) would reduce transfusion requirements compared with rFVIIa after 8 units (late).**

Methods: **We retrospectively reviewed records for trauma admissions to combat support hospitals in Iraq between January 2004 and October 2005. Patients requiring a massive transfusion and receiving rFVIIa were identified. Groups were divided into those who received rFVIIa early or late.**

Results: **Of 5,334 trauma patients (civilian and military), 365 (6.8%) required massive transfusion. Of these, 117 (32%) received rFVIIa. Complete records for blood transfusions were available for 61 patients: 90% had penetrating trauma, 17 received rFVIIa early, and 44 received it late. At admission, temperature, heart rate, blood pressure, Glasgow Coma Scale score, base deficit, hemoglobin, platelets, prothrombin time/International Normalized Ratio, and Injury Severity Score were similar in both groups as were administered units of fresh frozen plasma, fresh whole blood, cryoprecipitate (cryo), and crystalloid. The early rFVIIa group required fewer units of blood during the first 24-hour period (mean 20.6 vs. 25.7, $p = 0.048$) and fewer units of stored red blood cells (mean 16.7 vs. 21.7, $p = 0.049$). Early and late mortality (33.3% vs. 34.2%, $p =$ NS), acute respiratory distress syndrome (5.9 vs. 6.8%, $p =$ NS), infection (5.9% vs. 9.1%, $p =$ NS), and thrombotic events (0% vs. 2.3%, $p =$ NS) were similar.**

Conclusions: **Early administration of rFVIIa decreased red blood cell use by 20% in trauma patients requiring massive transfusion.**

Key Words: **Trauma, penetrating, recombinant factor VIIa, blood transfusion, massive transfusion, combat, coagulopathy.**

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Hemorrhage is the principal reversible cause of death after trauma[1,2] and the vast majority of deaths resulting from hemorrhage occur within the first 24 hours.[3,4] Although the majority of trauma patients do not require stored red blood cell (RBC) transfusion, a small percentage of trauma patients require massive transfusion (≥10 units RBC). Coagulopathy is frequently present in trauma patients upon presentation to the hospital.[5] This coagulopathy is known to be an independent predictor of mortality[6] and can be exacerbated by hypothermia and dilutional coagulopathy resulting from massive blood transfusion or fluid resuscitation.[7]

Dilutional coagulopathy is currently treated by transfusion of fresh frozen plasma (FFP), platelets (PLTs), and cryoprecipitate (cryo). Once dilutional coagulopathy develops, it is difficult to manage and evolves into a "bloody vicious cycle".[8,9] Such patients require further stored blood products that contribute to the underlying coagulopathy and result in further blood loss.[10] Agents that promote clotting are useful in situations where standard blood products are insufficient to control dilutional coagulopathy. A growing body of literature examines the safety and efficacy of one such agent, recombinant factor VIIa (rFVIIa; Novo Seven, Novo Nordisk A/S, Bagsvaerd, Denmark) in trauma.[11–15] A randomized clinical trial published in 2005 using rFVIIa in trauma patients revealed decreased blood product requirements in blunt injuries, although no improvement in survival was found.[16]

Increasingly, studies point toward the importance of early transfusion of clotting factors in preventing dilutional coagulopathy.[17,18] "Last ditch" administration of rFVIIa is considered ineffective[19] and it is has been proposed that earlier administration of rFVIIa might improve clinical response.[20] The military experiences in Iraq and Afghanistan have provided a unique opportunity to study the timing of rFVIIa usage in blast and high-velocity penetrating injuries. We hypothesized that earlier administration of rFVIIa would decrease transfusion requirements in trauma patients requiring massive transfusion.

PATIENTS AND METHODS

The data presented here were obtained under a human use protocol that received Institutional Review Board approval through the Department of Clinical Investigation at Brooke Army Medical Center in San Antonio, TX. Using the Joint Theater Trauma Registry (JTTR) maintained at the US Army Institute for Surgical Research (USAISR) at Ft. Sam Houston in San Antonio, TX, we performed a retrospective

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From the Hematology/Oncology Service Department of Medicine, Walter Reed Army Medical Center (J.G.P.), Washington, DC; the Trauma/Critical Care Section, Oregon Health & Science University (M.A.S.), Portland, OR; and the United States Army Institute of Surgical Research (C.E.W., J.B.H.), San Antonio, TX.
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Address for reprints: Jeremy G. Perkins, MD, Walter Reed Army Medical Center, 6900 Georgia Ave, NW, Washington, DC 20307; email: jeremy.perkins1@us.army.mil.

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analysis of data for trauma patients admitted to two combat support hospitals (CSH) in Iraq between January 2004 and October 2005. The JTTR is a database established by the Department of Defense to capture data prospectively from multiple nonintegrated clinical and administrative systems. This database provides comprehensive data collection from the point of injury through discharge from military treatment facilities for coalition and foreign national patients and from point of injury through rehabilitation for US patients.

Patients were identified who received a massive transfusion, defined as 10 or more units of red blood cells (including both stored RBC and fresh whole blood units) in 24 hours[10] and who also received rFVIIa. Stored blood products (RBCs, FFP, and cryo) were obtained from the United States via the Armed Services Blood Program. Apheresis platelets were collected from healthy donors at the hospital and emergency whole blood unit collections were donated by healthy volunteers as previously described.[21] A massive transfusion protocol was in place for the hospital to guide resuscitation.[21] Two groups were defined and evaluated: patients receiving rFVIIa before receiving ≤8 units of blood (early) and patients receiving rFVIIa after an initial 8 units of blood (late). The cutoff of 8 units was chosen based on the current multicenter, multinational prospective randomized trial studying the efficacy of rFVIIa after trauma.[22] Patients must receive rFVIIa before completion of the eighth unit to be eligible for this trial. After identification, patient charts were evaluated for admission vital signs, Glasgow Coma Scale (GCS) score, laboratory tests, documented injuries, blood product administration (stored RBC, fresh whole blood [FWB], FFP, cryo, and PLT), dosage and timing of rFVIIa administration, survival after 48 hours, survival at the combat hospital, and survival at 30 days after evacuation to higher levels of care. Abbreviated Injury Scales scores and Injury Severity Scores (ISS) were calculated by trained staff using ISS98[23] after patient discharge.

The primary outcome evaluated was survival. Inhospital survival was defined as survival at the combat support hospital in Iraq. For 30-day survival assessment, the majority of patients were either US soldiers who could be tracked as they reached higher echelons of care or casualties who spent a prolonged period of time at the hospital. Iraqi and civilian casualties who were discharged before 30 days and had incomplete follow-up to ascertain survival were excluded from the 30-day survival analysis. The available combat hospital inpatient records, cultures, and radiologic reports were evaluated for secondary outcome measures including blood transfusion requirements and the clinical diagnoses of acute respiratory distress syndrome (ARDS), infection, deep venous thrombosis (DVT), pulmonary embolism (PE), and stroke.

Statistical analysis was performed with SPSS 13.0 (Chicago, IL). Statistical significance was set at a $p \leq 0.05$ throughout. Data within groups were considered nonparametric and comparisons were made using Mann–Whitney U and Fisher's exact tests. Data are presented as median (range) [mean].

RESULTS

During the 22-month period between January 2004 and October 2005, the CSH received 5,586 patients from both civilian and military populations with traumatic injuries, of whom 252 were dead on arrival (no vital signs, no procedures/blood transfusions, declared dead in emergency department). Of the 5,334 patients (civilian and military) alive on arrival, 1,348 (25%) patients were transfused: 365 (6.8%) were identified as having received 10 or more units of red blood cells at the hospital. Of the massively transfused patients, 117 (32%) were documented as having received rFVIIa. Eighty-one of these patients had clinical records available for review. Twenty patients did not have clear time documentation of rFVIIa administration and were excluded from further analysis. Of those meeting study criteria, 17 patients received rFVIIa early (before receiving ≤8 units) and 44 patients received rFVIIa late (after receiving >8 units) in their resuscitation.

At admission (Table 1), there were no differences between early and late groups in admission characteristics for age, weight, mechanism of injury, Injury Severity Score, heart rate, systolic or diastolic blood pressures, temperature, GCS score, pH, base deficit, hemoglobin, platelet count, prothrombin time, International Normalized Ratio, creatinine, or intubation upon arrival to the emergency room.

The median dose of rFVIIa administered was 9.6 mg for both groups (p = NS) and median dose per kilogram of body weight was 105 μg/kg (early group) versus 110 μg/kg (late group; Table 2). The early rFVIIa group received rFVIIa after a mean 5.7 units and the late rFVIIa group received rFVIIa after a mean 14.0 units ($p < 0.001$). The statistical difference between groups is explained by how the groups were defined (early ≤8, late >8 units of blood). When compared with the late rFVIIa group, the early rFVIIa group required fewer units of blood during 24 hours (mean 20.6 versus 25.7, $p = 0.048$), a 22% reduction in blood transfusions. Fewer stored RBC units were transfused to the early rFVIIa group in the first 24 hours as compared with the late rFVIIa group (mean 16.7 vs. 21.7, $p = 0.049$). There were no differences in the 24-hour requirements for whole blood, FFP, cryoprecipitate, or platelet units. There was also no difference in requirements for crystalloids.

The incidence of late complication including ARDS, infection, and thrombotic events (DVT, PE, stroke) was not different between groups (Table 3). Eight patients (two in the early group and six in the late group) were lost to follow-up and were excluded from the 30-day survival analysis. There was no difference in survival (Table 4) between the early and late groups at 48 hours (82.4% vs. 81.8%, $p = 0.36$), inhospital (70.6% vs. 77.3%, $p = 0.79$), or at 30 days (66.7% vs. 65.8%, $p = 0.58$).

DISCUSSION

To the best of our knowledge, this is the first article to examine the impact of the timing of rFVIIa administration in

Table 1 Characteristics at Admission

	Early rFVIIa (≤8 units blood)	Late rFVIIa (>8 units blood)	*p* Values
n	17	44	
Age (years)	22 (20–30)	23.5 (17–43)	0.82
Weight (kg)	77.5 (37–110)	80 (60–120)	0.86
Penetrating injury	88%	91%	1.00
Injury Severity Score	16 (9–43)	18 (9–59)	0.48
Heart rate (bpm)	100 (60–144)	105 (63–150)	0.36
Systolic blood pressure (mm Hg)	105.5 (78–175)	93 (45–225)	0.15
Diastolic blood pressure (mm Hg)	58 (30–94)	50 (26–102)	0.09
Temperature (°F)	96.0 (91.8–100.5)	96.0 (89.2–100.0)	0.60
Glasgow Coma Scale score	7 (3–15)	14 (3–15)	0.34
pH	7.21 (6.95–7.39)	7.20 (6.50–7.46)	0.99
Base deficit (mEq/L)	9.5 (0–15)	8 (0–26)	0.75
Hemoglobin (g/dL)	12.5 (6.0–17.0)	10.7 (6.0–18.0)	0.46
Platelets ($\times 10^9$/L)	211 (35–341)	188 (8–462)	0.89
Prothrombin time (seconds)	15.4 (5.9–52.9)	16.2 (9.2–45.8)	0.58
International Normalized Ratio	1.42 (0.90–6.00)	1.63 (0.90–9.00)	0.44
Creatinine (mg/dL)	1.1 (0.7–2.1)	1.4 (0.8–2.0)	0.32
Estimated blood loss (mL)	2,500 (700–8,000)	3,200 (1,000–14,000)	0.58
Intubated before arrival	44%	33%	0.39

Data are expressed as median (range) or percent. *p* values were determined by Mann–Whitney U test or Fisher's exact test.

trauma casualties receiving massive transfusion. Our findings suggest that rFVIIa administered early in the process of massive transfusion reduces 24-hour total blood unit requirements. Giving the drug earlier may allow it to be more active, as there is less dilution of clotting factors and platelets that are known to develop during the course of resuscitation.[20] Of additional importance, we were able to show these benefits in patients with injury from penetrating trauma, which accounted for the vast majority of injuries (~90%) in this study. Previously, Boffard et al.[16] were unable to demonstrate a significant decrease in RBC unit requirements in patients with penetrating trauma in a clinical trial examining the effect of rFVIIa. Of note, all patients in the Boffard study were dosed with rFVIIa after 8 units of RBC. As in the current and previous randomized controlled rFVIIa trauma studies, the drug was given after a certain number of units of blood, not after a time frame. In the current study, requirements for other blood products like FWB, FFP, PLT, and cryo were not diminished. Additionally, no survival benefit (Table 4) was noted in massively transfused patients receiving rFVIIa early, as compared with late rFVIIa administration.

This study had a low incidence of late complications (Table 3), similar to other reported trials.[16,24] There was no difference in the rates of ARDS and infection between the early and late groups, though the study size was small. Thrombosis has also been suggested as a concern in patients receiving rFVIIa.[25,26] Although not documented in this study, patients routinely received prophylaxis against thromboembolism because of the known high incidence of such events in patients with traumatic injury if not treated with prophylaxis.[27] There was only one thrombotic event documented in this study, occurring in a patient with a penetrating wound to the thorax with a large pulmonary contusion. This patient received rFVIIa intraoperatively 75 minutes after arrival to the hospital and after receiving 21 units of blood and 12 units of FFP. This patient developed a left-sided thrombotic stroke complicated by herniation on hospital day 5. The low reported occurrence of thromboembolic events may be

Table 2 Recombinant Factor VIIa Dose, Blood Products, and Crystalloid Usage

	Early rFVIIa (≤8 units blood)	Late rFVIIa (>8 units blood)	*p* Values
Dose rFVIIa (mg)	9.6 (4.8–19.2)	9.6 (4.8–19.2)	0.8
Dose/kg (mcg/kg)	105 (70–240)	110 (40–270)	0.9
24-hr total blood units (RBC + FWB)	18 (12–44) [20.6]	23 (10–58) [25.7]	0.048
Stored red blood cells (RBC)	14 (7–32) [16.7]	20.5 (9–46) [21.7]	0.049
Fresh whole blood (FWB)	0 (0–21) [3.9]	2.5 (0–26) [4.0]	0.5
Fresh frozen plasma	8 (2–25) [10.7]	10.5 (0–40) [13.1]	0.3
Cryoprecipitate	10 (0–30) [12.0]	10 (0–52) [15.2]	0.4
Platelet transfusion	0 (0–6) [1.0]	0 (0–7) [1.2]	0.8
24-hour crystalloid (L)	10.8 (4.4–17.5) [11.2]	10.9 (3.6–20.5) [11.0]	0.8

Data are expressed as median (range) [mean].

Table 3 Late Complications

	Early rFVIIa (≤8 units blood)	Late rFVIIa (>8 units blood)	*p* Values
n	17	44	
Acute respiratory distress syndrome	1 (5.9%)	3 (6.8%)	1.00
Infection	1 (5.9%)	4 (9.1%)	1.00
Deep vein thrombosis/pulmonary embolism/stroke	0 (0.0%)	1 (2.3%)	1.00

Data are expressed as n (%). *p* values were determined by Fisher's exact test.

because of lack of screening and incomplete documentation, although it may also be reflective of the relatively young and healthy population.

Although massive transfusion occurs in only a small minority of patients, this group often requires extensive blood banking resources.[28] The total number of blood units needed to completely resuscitate the casualties in the early rFVIIa group was diminished by a mean of 5.1 units (22%). Although this study did not show a survival benefit, it is well documented that increased exposure to blood products increases the risk of infection,[29] multiorgan failure,[30,31] and mortality.[32] The US Food and Drug Administration has acknowledged that decreased blood transfusion is an appropriate end-point when considering the evaluation of resuscitation interventions.[33] This study suggests that early administration of rFVIIa in patients who are anticipated to require massive resuscitation could potentially reduce blood requirements by 22%. In austere environments or during mass casualty events that stress a hospital's resources, early administration of rFVIIa could limit the number of blood products required to manage patients.

Limitations to this study should be noted. This was a retrospective analysis of relatively small numbers of patients. As such, this study is hypothesis generating and it is difficult to draw firm conclusions. The complications of ARDS and thromboembolic events were based on clinical diagnoses with supporting radiographic studies. No formal criteria were followed to establish the diagnosis of ARDS and there was no systematic evaluation for asymptomatic thromboembolic events. It is difficult to maintain accurate and complete documentation of patient complications in the combat environment. In addition, only recently have systematic processes been implemented to capture complications that occur after evacuation or transfer to other hospitals. Mortality in this study was known for US casualties evacuated to higher echelons of care. However, this study did not report on ventilator days, intensive care unit days, or hospital days because many US casualties were evacuated early in their hospital course and these outcome measures were not available. Prospective studies with larger numbers of patients using formal criteria for ARDS and screening for thromboembolism would help to clarify differences in mortality and complications between groups.

Table 4 Survival

	Early rFVIIa (≤8 units blood)	Late rFVIIa (>8 units blood)	*p* Values
48-hour survival	14/17 (82.4%)	38/44 (81.8%)	0.36
Inhospital survival	12/17 (70.6%)	34/44 (77.3%)	0.79
30-day survival	10/15 (66.7%)	25/38 (65.8%)	0.58

Data are expressed as n (%). *p* values were determined by Fisher's exact test.

An ongoing multicenter, multinational prospective randomized trial studying the efficacy of rFVIIa after trauma is being conducted in which patients must receive rFVIIa before completion of the eighth unit of blood to be eligible.[22] However, based on the preliminary data supplied by the current study, early administration of rFVIIa (≤8 units blood) during massive resuscitation is supported.

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DISCUSSION

Dr. Kenneth D. Boffard (Johannesburg, South Africa): Coagulopathy causes mortality, and unfortunately, in trauma, there is an awful lot more not known than known. It's widely accepted that early administration of cryo, FFP, and platelets may correct this early coagulopathy.

It's also widely accepted that we're in danger of having a number of people saying, "Don't confuse me with the facts. I know what I think". Factor VIIa has been used increasingly off-label as an adjunct to assisting the clotting cascade, sometimes, with dramatic results and sometimes with results almost as good as those perceived by the authors.

This military retrospective study looked in a 22-month period at a large group, some 5.5 thousand patients, 365 of whom received massive transfusion, defined as >10 units of blood in 24 hours, and 117 of those received Factor VIIa.

They were divided into the groups who received blood early or the Factor VIIa early and late. Again, since Factor VIIa is an adjunct to clotting, conceptually, it is very nice to say it works not on its own but with a number of other substances, and the earlier we give it the better it is likely to be.

Full records of those 117 were only available for 61; two-thirds of those were given in the late group, who were the late recipients. There was no difference in mortality.

What is significant is patients in the earlier group required or seemed to require 22% less blood if Factor VIIa was administered. This equated to a saving of more than 5 units of blood.

Again, this is extremely attractive in the military context. However, the study is limited in that the numbers studied during the time period were too small to examine mortality complications. Ventilator days were not assessed as qualitatively as it was possible to do.

The more substrate you have, the better it works. I'd like to pose a couple of questions to the authors. First, this was a retrospective study, was any attempt made to compare the study group, particularly the early receivers, with a control, in other words, the remaining people who did not have the drug administered?

Of the 365 patients, only 117 were dosed, and I'd like to know what the criteria for doing this actually were. Also, how did the outcomes in and baseline characteristics of the nondosed group compare with those of the dosed group and with the control group? Finally, while accepting that it is a military organization, was there a consent process and was this in any way influential in grouping two-thirds of the patients into the late group?

Dr. Martin A. Schreiber (Portland, Oregon): I'd like to reiterate, and I think this will answer several of the questions, this was a retrospective study. And there was no intention at the time of this data collection to actually do this work in terms of determining the effects of early versus late recombinant Factor VIIa use.

What we did have was a lot of data on a lot of patients with severe injuries. We had a lot of patients who received massive transfusions and we decided later that a very important question would be to look at this. So, we did not prospectively seek to answer this question when the study was performed.

In terms of the massive transfusion protocol and the criteria for giving Factor VII, this was completely physician and surgeon dependent. When individuals thought that the patient was having a coagulopathy, it would not be rapidly

corrected by our massive transfusion protocol, and Factor VII was given.

I will also tell that during the course of the study, the practice of giving Factor VII changed. If I were to show you the massive transfusion protocol again, as it is practiced today, the Factor VII is going in with those first units of FFP and packed red blood cells. So actually, during the course of the study, the practices have changed, and Factor VII is being used much more aggressively because of the better efficacy when it is given early. So, this was not an intended outcome of the study.

In terms of the consent process, this was not considered a study at the time. Basically, this is an observational study so we did not obtain consent for entering patients into the study.

Data was collected prospectively and Institutional Review Board approval was given by the Brooke Army Medical Center to analyze the data.

So, although we did not obtain consent, we do have IRB approval for this study and many other studies to look at the results of these events.

Dr. David P. Blake (Misawa, Japan): In your data that you presented, the GCS scores of the two groups did differ, although they were not statistically significantly. Do you think that was a result of the group sizes and the power of the study in this particular case?

Secondly, what do you think is the role that Factor VIIa is actually playing? Do you think this is a result of the tissue factors that are being released, or do you think there is some other more direct component that is contributing to this better coagulation control down the road?

Dr. Martin A. Schreiber: In terms of your second question, I think as far as we know, the mechanism of Factor VII has been well described.

There is a tissue factor dependent and a tissue factor independent mechanism. I think, in these particular patients, that there is massive tissue factor release, as you can see by these blast injuries. I also think that the tissue factor pathway is playing a major role.

I think that the drug is especially effective in this study because of the aggressive use of blood products, especially the use of early fresh whole blood. When the Factor VII has been given, platelets are present, fibrinogen is present in significant quantities, and the drug has a good opportunity to work. So I think that primarily this is working by a tissue factor-dependent mechanism in this highly tissue factor-dependent group. And I think that it works well because of the good presence of other factors.

Dr. Richard Dutton (Baltimore, Maryland): One simple question: Did the patient with the complication have a carotid injury, and do you have any way of knowing?

Dr. Martin A. Schreiber: There was a CT scanner present. That patient did not have a diagnosed carotid injury but it's possible that he did. That patient did not have a carotid injury ruled out, so it is unknown. He did not have a CTA of his carotid to rule it out.

Dr. Richard Dutton: Are the penetrating injuries that you showed and that you're treating any different than high-energy civilian blunt trauma?

Dr. Martin A. Schreiber: I'd say emphatically yes to your second question. I think that 80% to 90% of the injuries that we're taking care of are motor vehicle crashes.

A 50 mile-per-hour motor vehicle crash is very, very different than the type of injury that an innovative explosive device creates. It is not atypical for us to see patients in Iraq with both their legs blown off; some of their arms blown off, and combined chest and abdominal injuries. So I think that the force of impact is many orders of magnitude higher in these types of injuries than what we're seeing in the civilian world, so emphatically, yes, there is a big difference.

Dr. Frederick A. Moore (Houston, Texas): It appears that you are fairly aggressive in administrating cryoprecipitate early in the resuscitation. In a recent study (presented at the Shock Society), we (in collaboration with John Holcomb and Charlie Wade) compared our civilian blunt trauma patients who get a massive resuscitation with the soldiers in Iraq who get a massive transfusion and found that upon arrival in the trauma receiving unit, these two groups had very similar profiles in regard to risk of developing coagulopathy and subsequent clinical course. In a different study (presented at the last Western Trauma Association) we analyzed prospectively collected data of patients who entered our massive transfusion protocol and observed that when these patients arrived in the ICU (approximately 6 hours after trauma center admission), only 10% had a fibrinogen level $<$100,000 mg/dl and 3% had a fibrinogen $<$50,000. The mean ICU admission level was roughly 140,000 and rapidly rose to 400,000 in the first 24 hours. Although we will administer cryoprecipitate in a bleeding patient when fibrinogen is $<$100,000, most blood bankers recommend cryoprecipitate only when fibrinogen falls below 50,000. Low fibrinogen does not appear to be a big problem in our severe blunt trauma patients, who are receiving a massive transfusion. I think these patients are similar to wounded soldiers in Iraq. Can you provide the rationale or the evidence for early cryoprecipitate administration in these wounded soldiers?

The second comment relates to the fact that a lot of your patients appear to be very acidotic. There is some controversy in the literature about whether Factor VIIa actually works in an acidotic environment. Do you aggressively try to correct acidosis prior to administering Factor VIIa?

Dr. Martin A. Schreiber: One of the things that we've done in our data collection, and hopefully, we'll be seeing some of this data early, is take a look at the admission laboratory studies on these patients, who are being admitted with massive trauma.

In the patients who are getting up to 20 units of blood ultimately within a 24-hour period, we are seeing that the mean INR is somewhere around 2 and the fibrinogen at admission is $<$100.

So there is a massive consumptive process that is going on with these massive trauma patients that is present usually within 30 to 90 minutes after injury in the absence of any significant fluid resuscitation.

So based on the admission laboratory studies that we're seeing in this patient population, we do think that the early use of the FFP and the cryoprecipitate is indicated.

In terms of your question about acidosis, the answer is yes. In patients who are acidotic, aggressive correction of the acidosis is performed in order to allow the Factor VII to be effective.

Ultimately, all of these patients are intubated early after their arrival in the medical treatment facility. Now, some of these patients that you're seeing with their legs blown off and these extremity injuries come in not intubated and they're talking to you. So, early after admission they're intubated and their acidosis is rapidly corrected, using the ventilator so that the Factor VII can be used effectively.